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CHAPTER 6. LOW YIELD CIGARETTES AND THEIR ROLE IN CHRONIC OBSTRUCTIVE LUNG DISEASE

CONTENTS

Introduction

Following the initial reports in the early 1950s linking cigarette smoke with lung cancer, the pathogenic role of cigarette tar content received considerable emphasis. Because the tar fraction of the smoke contained the bulk of the carcinogenic effect of whole smoke, and because lung cancer risk was closely related to other measures of total smoke exposure (number of cigarettes smoked per day, depth of inhalation, etc.), it was suggested that risk might be related to the amount of tar generated by different cigarettes. This prompted health authorities to advise smokers who were unable to quite smoking to switch to low tar cigarettes (U.S. Senate 1967; Health Department of the United Kingdom 1976). To facilitate this process, the Federal Trade Commission published smoking-machine assays of the tar and nicotine yield of different cigarette brands (Pillsbury et al. 1969). This approach to low tar and nicotine cigarettes was based on the assumption that smoking lower yielding brands, as determined by a smoking-machine, would result in a proportional reduction in the lung's exposure to these toxic substances. This approach to "safer" cigarette smoking has been promoted by the tobacco industry and apparently accepted by the smoking public, as evidenced by the escalation in sales of low tar and nicotine cigarettes. However, there is increasing evidence that this concept of a "less hazardous" cigarette is misleading; although definitive studies are still awaited, it appears that switching from regular to low tar and nicotine cigarettes may not substantially reduce the risk of chronic airflow obstruction.

Problems of Measurement by Machine

The first step in evaluating the relative health risks of different cigarettes is to establish some standardized measure of the toxic substances in different cigarettes in order to facilitate comparison. Quantifying each of the several thousand constituents of cigarette smoke for each brand of cigarette, and assessing the changes in these constituents as the manufacturing and agricultural processes change, would be a truly herculean task; therefore, a more modest goal of quantifying tar and nicotine yields was accepted. To date, the yields determined by the Federal Trade Commission have been the most widely adopted. These measurements are obtained with a laboratory smoking-machine, which consists of a syringe pump that takes a 35 ml bell-shaped puff from a cigarette, over a 2-second period, once per minute until a predetermined butt length is reached, either 23 mm for nonfiltered cigarettes or 3 mm longer than the filter overwrap for filter-tipped cigarettes (Pillsbury et al. 1969). These parameters are based on observations of smoking patterns in seven subjects in Europe in 1933 (Kozlowski 1983). Today's cigarette

is markedly different from that smoked in 1967 when these parameters were established, yet the same parameters are still employed.

Measurements obtained using these parameters indicate a marked reduction in the tar and nicotine yield of cigarettes over the last decade (Figure 1). In addition to the actual tar and nicotine yield of the tobacco, the yield measured by a smoking-machine is influenced by many factors, including cigarette length and diameter, porosity of the cigarette paper, presence of a ventilated or an unventilated filter, butt length, number of puffs, interpuff interval, puff volume, puff duration, puff pressure profile, and frequency of puffing at different stages of cigarette consumption. The number of puffs is important in determining the tar yield of a cigarette, and the number of puffs taken from some brands with the official smoking-machine has significantly declined in recent years (Kozlowski 1981). Since puffs are taken at 1-minute intervals, a more rapidly burning cigarette will have a smaller number of puffs. The burning time of the cigarette is determined by porosity of the cigarette paper, the amount of tobacco in the cigarette, and the diameter of the cigarette column. In a survey of Canadian cigarettes between 1969 and 1974, Kozlowski et al. (1980b) noted a significant reduction in the number of puffs taken in the official assays over this time period, which was strongly correlated with a reduction in tar yield. Omission of the last few puffs can markedly affect tar yield, because tar delivery increases with each puff, and the last few puffs from a cigarette can contain twice as much tar as the first few puffs (Wiley and Wickham 1974). Currently published yields do not indicate the number of puffs taken, which may range from 7 to 12 and may result in a marked variation of the tar yield.

Ventilated cigarette filters, which cause inhaled smoke to be diluted with air, are one of the major methods of achieving low tar yields (Gori and Lynch 1978). Cigarettes with ventilated filters constituted about 25 percent of all cigarette sales in the United States in 1979 (Hoffmann et al. 1980). During systematic interviews, Kozlowski et al. (1980a) found that from 32 to 69 percent of low tar smokers block these filter perforations with their fingers or lips, a feature unaccounted for by smoking-machines. This hole blocking increased the yield of toxic products by 59 to 293 percent.

If a person smokes a cigarette in a manner identical to the smoking-machine, the delivery of tar and nicotine to the mouth will be the same as that estimated by the machine. Human smoking patterns are diverse, however, and show considerable variation from the machine parameters; puff volumes range from less than 20 ml to more than 90 ml (Tobin and Sackner 1982), compared with the fixed 35 ml volume employed by the machine. Differences in puff profile from the bell-shaped puff used by the machine also alter cigarette

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Tar mg   Nicotine mg
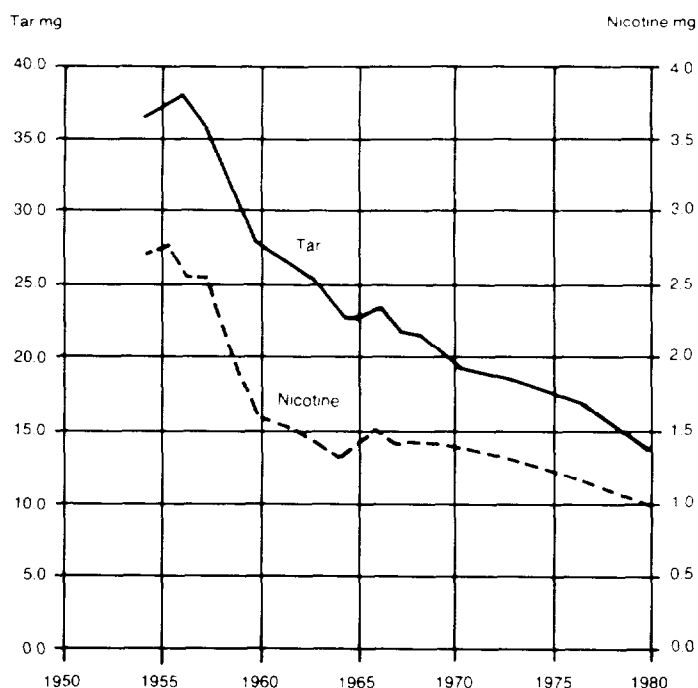
FIGURE 1.—U.S. sales-weighted average tar and nicotine
               yields
SOURCE: American Cancer Society (1981).

yield. Numerous studies indicate that smokers compensate for lower
yielding cigarettes by altering their style of smoking. For each
different cigarette brand, smokers may have a different smoking
pattern. To provide more meaningful information, smoking-ma-
chines should be designed to reproduce variations in the manner of
smoking each cigarette brand, and their assays should provide both
an average and a range of tar and nicotine yields depending on the
ndividual pattern of smoking (USDHHS 1981).

Many investigators have examined the relationship between the
machine-determined nicotine yield of a cigarette and the concentra-
ion of nicotine or its metabolites in blood or urine. A fair correlation
vas observed in some studies (Goldfarb et al. 1976; Herning et al.
983), but most studies have revealed a poor correlation (Russell et
l. 1975, 1980; Sutton 1982; Feyerabend 1982; Benowitz et al. 1983).
Machine-determined nicotine yield accounts for only from 4 (Russell
t al. 1980) to 25 percent (Herning et al. 1983) of the variation in
lood nicotine concentration, whereas 50 to 60 percent of the
ifferences in blood nicotine levels are attributable to individual

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smoking behavior. The overriding importance of the pattern of smoking in determining nicotine delivery from a cigarette was underlined in a recent study demonstrating that the nicotine content of the unburned tobacco was similar for cigarettes with high and low nicotine yields determined by smoking-machine assays (Benowitz et al. 1983).

The concept of providing the smoker with information on cigarette yield need not be abandoned. Smoking-machines can be designed to control the puff number, puff volume, puff pressure profile, puff duration, puff interval, butt length, position of the cigarette during and between puffs, and "restricted" or "free" smoking, i.e., whether the butt end is closed or open (Creighton and Lewis (1978a, b). These parameters should be determined and used to obtain an average and a range of yields for each brand. Measurement of cigarette yield should include assays not only of tar and nicotine but also of carbon monoxide and other toxic substances, because compensatory smoking behavior may alter the exposure to each substance beyond that expected on the basis of tar and nicotine delivery.

Effect of Low Tar and Nicotine Cigarettes on Cough and Phlegm Production and Development of Chronic Obstructive Lung Disease

Cigarette smokers account for the vast majority of deaths from chronic obstructive lung disease (COLD) (Peto et al. 1983), and the relative risk for the effects of smoking on mortality from COLD is even greater than that for lung cancer (see the chapter on Mortality in this Report). Chronic obstructive lung disease in smokers may take the following three forms: (1) cough and mucus hypersecretion, (2) airway obstruction, and (3) emphysema. Frequently the three components coexist, as all are related to cigarette smoking, but the agents in cigarette smoke responsible for each type of lung injury may be different. Over the past 25 years, considerable progress has been made in our understanding of the role of cigarette smoking in the pathogenesis and natural history of COLD, but most of the available data have not related lung function to cigarette yield.

Epidemiologic Studies

The cardinal importance of cigarette smoking in the pathogenesis of COLD has been repeatedly documented, and generally the severity of disease increases with increasing cigarette consumption (Ferris et al. 1976). Because of this dose–response relationship, it has been hoped that a reduction in cigarette yield by filtration or other means would reduce the risk of disease (Gori 1976). Available epidemiologic studies of the effect of low yield cigarettes on the development of COLD have shown variable results, which reflects

marked differences between the studies in terms of the population studied, sample size, variation in cigarette brands, reference period of the study, criteria of respiratory involvement, and type of statistical analysis, and whether the study was of a cross-sectional or a longitudinal design. Separating the studies by the three components of smoking-induced COLD indicates that there is a growing body of data on the effect of cigarette yield on the development of mucus hypersecretion and airway obstruction, but currently no information on the development of emphysema.

Several studies have examined the effect of cigarette yield on respiratory symptoms and have observed a relationship between reduction in cigarette yield and the prevalence of cough (Comstock et al. 1970; Freedman and Fletcher 1976; Fletcher et al. 1976; Dean et al. 1978; Schenker et al. 1982) and phlegm production (Comstock et al. 1970; Rimington 1972; Hawthorne and Fry 1978; Higenbottam et al. 1980b). Tar yield was not defined in some of these earlier studies (Comstock et al. 1970; Rimington 1972; Dean et al. 1978; Hawthorne and Fry 1978), but instead a comparison was made between smokers of plain cigarettes and smokers of filter-tipped cigarettes. The tar yield was specified in some studies: in the recent study by Schenker et al. (1982) it ranged from 0.4 to 28 mg; in the studies by Freedman and Fletcher (1976), from 17 to 20 mg; and in the studies by Higenbottam et al. (1980b), from 18 to more than 33 ing, higher than that observed in many of today's cigarettes. In a cross-sectional survey of over 18,000 men (Higenbottam et al. 1980b), the beneficial effect of low tar cigarettes on phlegm production was lost when subjects smoked 20 or more cigarettes per day, as their prevalence of phlegm production increased to that observed in higher tar cigarette smokers. In contrast, in another cross-sectional study of 5,686 women (Schenker et al. 1982), cigarette tar content was a significant risk factor for chronic cough and of borderline significance for phlegm production; this effect of cigarette tar content was independent of the number of cigarettes smoked per day. Chronic cough or phlegm production was approximately twice as common in smokers of high tar (at least 20 mg) cigarettes as it was in low tar (less than 10 mg) smokers. In the latter study, however, multiple logistic regression analysis indicated that the risk of chronic cough and phlegm production is more strongly affected by daily cigarette consumption than by tar content; these symptoms were 4.5 times more common in smokers of 25 or more cigarettes per day than in smokers of less than 15 cigarettes per day.

A small number of studies have examined the importance of cigarette yield on change in pulmonary function. In a prospective study of 680 men, Comstock et al. (1970) noted that smokers of plain cigarettes, compared with smokers of filter-tipped cigarettes, had a lower FEV_1 at entry into the study. Followup measurements showed
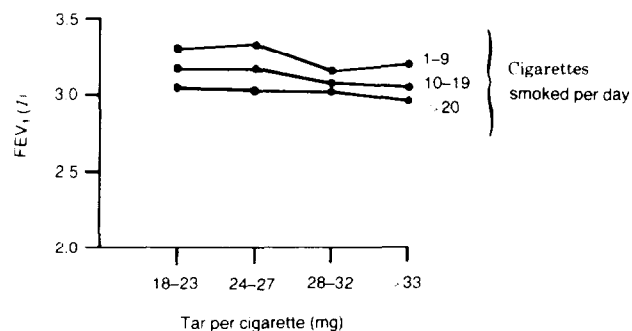
FIGURE 2.—Relationship between mean FEV₁ of
            asymptomatic smokers (adjusted for height and
            weight) and tar yield of cigarettes, by number
            of cigarettes smoked per day

a greater mean reduction of FEV₁ in users of filter-tips, so that the reduction was similar in the two groups after 5 to 6 years of followup. Unfortunately, the variance of the data was not stated, and tests of statistical significance were not performed. In another longitudinal survey of 1,355 men, Sparrow et al. (1983) determined the effect of cigarette tar content, which ranged from less than 16 mg to more than 22 mg, on pulmonary function. Multiple regression analysis indicated that tar content did not significantly influence baseline spirometry or repeat measurements after 5 years of followup. Cross-sectional epidemiologic surveys also indicate no relationship between abnormal pulmonary function and the use of filter-tipped versus plain cigarettes (Beck et al. 1981) or cigarette tar content (Higenbottam et al. 1980b) (Figure 2).

Interpretation of these studies as evidence that cigarette tar and nicotine yield is not an important factor in the development of COLD is premature. First, cross-sectional studies are limited in their capability of defining the natural history of a disease. Second, COLD has a very slow progress, and Fletcher et al. (1976) suggest that a span of approximately 8 years is necessary to establish rates of change of spirometric values with sufficient confidence even to distinguish between smokers and nonsmokers. Third, we have no information on the baseline pulmonary function of smokers at the time they choose between high or low tar and nicotine cigarettes. Significant differences in pulmonary function have been observed between young adults who decide to smoke and those who avoid cigarette smoking (Tashkin et al. 1983), and it is possible that similar

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function differences may exist in subjects who choose between high or low tar and nicotine cigarettes. Fourth, the yield of tar and nicotine used in many of these studies does not lie in the same range as that produced by many of today's cigarettes.

However, the possibility that cigarette tar content is related to the development of cough and phlegm, but not of dyspnea or airflow obstruction, is consistent with current concepts of COLD. In a study of 792 men followed over an 8-year period, Fletcher et al. (1976) observed that cigarette smokers were susceptible to two distinct chronic lung diseases—mucus hypersecretion and chronic airflow obstruction. This has recently been confirmed in a large prospective study (Peto et al. 1983) of 2,728 men, followed over 20 to 25 years, which showed that the risk of death from COLD was strongly correlated with initial degree of airflow obstruction, but bore no relationship to initial mucus hypersecretion.

Given the evidence that mucus hypersecretion may depend on the tar fraction of cigarette smoke, while development of airflow obstruction is more closely linked to the number of cigarettes smoked, Higenbottam et al. (1980b) reasoned that these differences might be due to a reduction in the particulate phase products, without a decrease in the gas phase products, in the low tar cigarettes. They hypothesized that tar droplets and soluble gases, such as sulfur dioxide and hydrogen cyanide, are more likely to be deposited or absorbed in the large airways where mucus is produced. The smaller airways, the earliest site of airflow obstruction, are exposed to a lower concentration of tar, but to a full concentration of insoluble gases such as nitrogen dioxide and ozone.

This line of reasoning is in agreement with several studies showing a reduction in lung cancer with the use of low tar and nicotine cigarettes (Wynder et al. 1970; Lee and Garfinkel 1981; Rimington 1981; Hammond et al. 1976). The tar fraction is the component of cigarette smoke particularly linked with the development of both lung cancer and mucus hypersecretion. Although clinicians have long linked chronic bronchitis (mucus hypersecretion) with emphysema, recent evidence indicates that mucus hypersecretion is not predictive of airflow obstruction, but is significantly greater in those smokers who develop lung cancer (Peto et al. 1983).

Mechanisms of Lung Damage

Studies of the mechanism of cigarette-smoke-induced lung damage have contributed significantly to the present understanding of COLD. Cigarette smoke may initiate and aggravate lung injury by a number of mechanisms and may also interfere with the lungs' defense responses.

These mechanisms include the protease-inhibitor imbalance theory for the pathogenesis of emphysema whereby alveolar wall

digestion results from an excess of proteases, a deficiency of their inhibitors, or a combination of both factors (see the chapter on Mechanisms in this Report). The sources of endogenous proteases include polymorphonuclear neutrophils and alveolar macrophages, both of which are found in increased number in the lungs of cigarette smokers. Protease release from both macrophages and neutrophils is increased in the presence of cigarette smoke (Rodriquez et al. 1977; Blue and Janoff 1978). In health, proteases are continually inhibited by α_1-antitrypsin, whereas proteases cause unimpeded digestion of lung tissue in patients with α_1-antitrypsin deficiency, with a markedly increased risk of emphysema. In addition to increasing the protease burden, cigarette smoke causes a functional inhibition of α_1-antitrypsin through the action of oxidants in cigarette smoke (Janoff et al. 1979).

The relative potency of smoke from cigarettes of varying tar and nicotine yields in stimulating protease production and release and in inhibiting α_1-antitrypsin has received scant scientific investigation. Travis et al. (1980) tested the effect of both filtered and unfiltered cigarette smoke on the elastase inhibitory activity of α_1-antitrypsin. Filtered smoke reduced elastase inhibitory activity by 3 percent, and a 19 percent reduction was observed with unfiltered smoke; the tar content of the respective smokes was not stated. The researchers reasoned that this small in vitro effect would be greatly magnified by in vivo conditions in the lung, particularly through its huge surface area. In addition to examining the effect of filters, Cohen and James (1982) recently examined the effect of tar and nicotine content on the elastase inhibitory capacity of α_1-antitrypsin. The oxidant capacity of cigarette smoke was also examined using a chromogenic electron donor. Aqueous condensates of cigarette smoke were obtained from a variety of brands ranging in tar content from about 1 mg to more than 20 mg. Reported tar and nicotine content correlated well with the amount of measured oxidants and the ability of a brand to reduce the elastase inhibitory capacity of α_1-antitrypsin. Filters were found to remove 73 percent of the oxidants from the aqueous smoke solutions. While these findings suggest that low tar and nicotine or filter-tipped cigarettes could reduce a smoker's predisposition to enzymatic lung damage and consequent COLD, it should be noted that neither study examined the effect of lower yield cigarettes on protease production. Morosco and Gueringer (1979) demonstrated a greater increase in elastase in dogs exposed to high nicotine cigarette smoke compared with low nicotine cigarette smoke. More important, these studies have not taken into account the compensatory changes in smoking pattern likely to result with lower yield cigarettes.

The airway response to acute exposure to cigarette smoke has been examined by several investigators employing spirometry (Da Silva and Hamosh 1981), body plethysmograph (Nadel and Comroe 1961),

and breathing pattern analysis (Tobin et al. 1982a). Airway narrowing has been consistently observed by some investigators (Nadel and Comroe 1961; Sterling 1967; Tobin et al. 1982a), but others report a variable response (Higenbottam et al. 1980a; Rees et al. 1982). In some studies, the acute airway response was unrelated to cigarette yield (Higenbottam et al. 1980a), but in most investigations (Robertson et al. 1969; Tobin et al. 1982a; Rees et al. 1982), smoking a low tar or filter-tipped cigarette induced less acute bronchoconstriction. The acute airway response is probably localized to the larger airways, as acute cigarette exposure resulted in no change in the nitrogen washout test of small airway function (Da Silva and Hamosh 1973; Tobin et al. 1982a). These observations on the relative bronchoconstrictor response of various types of cigarettes may be important in our understanding of why some smoking novitiates persist with the habit despite the initial unpleasant reactions (Tashkin et al. 1983), but it is unlikely that repeated episodes of smoking-induced acute airway narrowing finally result in COLD.

Future studies examining the mechanism of smoking-induced lung injury must not only take into account the range of cigarette yields, as determined by a smoking-machine, but also consider variations in smoking behavior. Puff volumes may vary considerably with nominal cigarette tar and nicotine content, thus altering the relative amount of various toxic substances yielded by different cigarettes. Similarly, inhalation profiles are of a diverse nature (Tobin et al. 1982b) and are likely to significantly alter the distribution, penetration, and retention of cigarette smoke constituents in the lungs.

Variation in Smoking Pattern With Switching to Low Tar and Nicotine Cigarettes

Low tar and nicotine cigarettes have gained considerable popularity among the smoking public, partly on the premise that a reduction in the nominal tar and nicotine yield results in a proportional reduction in the health hazards of cigarette smoking. The validity of this approach to cigarette smoking is contingent on the accuracy of smoking-machines in reflecting the actual manner of puffing and also on the smoker not altering smoking behavior to compensate for variations in nominal tar and nicotine content. Should smokers develop compensatory alterations in their smoking behavior, this would not only reduce the relevance of the smoking-machine assays but might also alter the proportionate delivery of the different toxic substances in cigarette smoke and expose the smoker to concentrations beyond those predicted by the smoking-machine.

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Smoking Behavior

Nearly 40 years ago, Finnegan et al. (1945) studied the effect of alterations in cigarette nicotine content on smoking behavior and noted no change in cigarette consumption. It is only in the last decade, with the increasing popularity of low tar and nicotine cigarettes, however, that this question has attracted significant interest. The results of 38 studies examining alterations in smoking behavior with a reduction in cigarette yield are shown in Table 1. Considerable differences can be observed between the studies, partly reflecting variations in the level of cigarette yield reduction, alterations in other cigarette constituents, type and duration of switching procedure, parameters evaluated, and techniques used in their measurement.

Most studies agree that smokers rarely increase their daily cigarette consumption upon switching from higher to lower yield brands. Reports are almost equally divided as to whether a smoker increases the number of puffs per cigarette or shows no change on switching to a lower yielding brand. There is an almost unanimous consensus that smokers take a larger puff volume from a lower yielding brand. Studies of puff volume also indicate huge variation between individual subjects (Guillerm and Radziszewski 1978; Herning et al. 1981; Tobin and Sackner 1982; Herning et al. 1983) and that considerable increases in puff volume may occur on switching from a higher to a lower yielding brand, with certain subjects increasing their puff volume by up to 75 percent (Tobin and Sackner 1982). This compensatory increase in puff volume may be observed within a single experimental session (Tobin and Sackner 1982) and maintained over several weeks (Rawbone et al. 1978; Stepney 1981). Full compensation for a lower yielding cigarette is generally not achieved by smokers taking a large puff volume (Rawbone et al. 1978; Herning et al. 1981; Tobin and Sackner 1982).

Instrumentation is required to quantitatively assess the pattern of smoking, but it is important to realize that such instrumentation may, in itself, alter usual smoking behavior. Puff volume has been almost universally measured by using a specialized cigarette holder incorporating different flowmeter designs (Frith 1971; Adams 1977; Rawbone et al. 1978). These devices consist of two tubes connected to a pressure transducer that measures the pressure drop across a small resistance (a filter insert) in the holder; the flow measured is integrated to obtain volume. Use of a cigarette holder has been shown to increase the rate of puffing and puff volume, compared with measurements made with the cheek inductive plethysmography coil (Tobin and Sackner 1982).

Unlike the compensatory increases in puff volume, measurements of the subsequent inhalation volume—which includes the volume of smoke mixed with air inhaled into the lung—have shown no change

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TABLE 1.—Effect of smoking low yield cigarettes on smoking pattern

First author	Reference year	Experimental design	Number of cigs smoked	Number of puffs/cig	Puff volume	Volume of inhalation	Duration of inhalation	CO parameters COHb	Expired CO	Relationship to nominal yield	Nicotine parameters Nicotine/cotinine level (blood/urine/saliva)	Mouth exposure index	Relationship to normal yield
Finnegan	1945	CS	NC										
Ashton	1970	VCF		↑								↑	Poor
Frith	1971	CS			↑								
Cohen	1971	CS						NC		Poor			
Russell	1973	CS	↑					↓		Good			
Turner	1974	CS						↓/NC		Poor			
Russell	1975	CS	↑								↓/NC		Poor
Goldfarb	1976	CS	↑								↓		Good
Forbes	1976	CS										↓	Good
Adams	1977	CS	NC	NC	NC								
Wald	1977	SVS						↑					
Sutton	1978	VCF	NC					↓		Poor	↓		Fair
Rawbone	1978	CS		NC	↑	NC						↓	Poor
Schulz	1978	CS	NC		↑								
Creighton	1978a,b	S			↑								
Adams	1978	CS		↑	↑								
Guillerm	1978	CS		↑	NC	NC		↑		Poor			
Jarvik	1978	CS	↑	↑									
Ashton	1979	CS	NC					•		Poor	↓	•	Poor
Garfinkel	1979	SVS	NC										
Hill	1980	CS						NC		Poor	•		Good
Robinson	1980	SVS										↓	Good
Russell	1980	SVS									NC		Poor
Henningfield	1980	VCF	NC	↑				↑	NC				
Wald	1980	SVS						↑					

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TABLE 1.—Continued

First author	Reference year	Experimental design	Number of cigs smoked	Number of puffs/cig	Puff volume	Volume of inhalation	Duration of inhalation	COHb	Expired CO	Relationship to nominal yield	Nicotine/cotinine level (blood/urine/saliva)	Mouth exposure index	Relationship to normal yield
								CO parameters			**Nicotine parameters**		
Herning	1981	CS		NC	↑				↑				
Wald	1981	SVS	NC					↑		Poor			
Stepney	1981	CS	NC	↑	↑				↓	Fair	↓	↓	
Jaffe	1981	SVS	NC/↑						NC	Poor			
Tobin	1982	CS		NC	↑	NC	NC						
Battig	1982	SVS	NC		↑				NC				
Sutton	1982	SVS			↑					Good			Poor
Griffiths	1981	CS		NC	↑								
Jaffe	1982	CS	NC/↑						NC	Poor			
Feyerabend	1982	SVS											Poor
Herning	1983	CS											Fair
Benowitz	1983	SVS											

NOTE: CS - controlled switching; VCF = variable cigarette filters; SVS = spontaneous voluntary switching; NC = no change; ↑ = increase, ↓ = decrease; CO = carbon monoxide.

on switching to a low yield cigarette. Likewise, in one short-term study (Tobin and Sackner 1982), duration of inhalation showed no relationship to nominal cigarette yield. Perhaps compensatory changes in inhalation parameters require a longer period of time than puff volume does.

Measurement of carboxyhemoglobin (COHb) concentration has been proposed as an index of the pattern of inhalation (Wald et al. 1975, 1978). While COHb provides valuable information on the amount of carbon monoxide absorbed from the lung during compensatory alterations in smoking behavior, it is an indirect index and provides complementary information on cigarette smoke inhalation rather than replacing direct measurements of the volume of inhalation.

Carbon Monoxide Uptake

Unlike tar and nicotine, which are present in the particulate phase, carbon monoxide (CO) is a constituent of the vapor phase of cigarette smoke. For this reason, cigarettes purported to produce a low tar and nicotine yield may not necessarily provide a lower yield of carbon monoxide. Compared with tar and nicotine yield, carbon monoxide yield is more dependent on cigarette design, including such features as paper porosity and perforations in the filter tips. These factors regulate the dilution of smoke with air and the burning profile of the cigarette, and thus can significantly reduce carbon monoxide yield. Wald (1976) showed that the carbon monoxide yield of filter-tipped cigarettes was 28 percent higher than that of plain cigarettes, although the average nicotine yield was lower in the filter-tipped cigarettes. He reasoned that smoke passing through a cigarette is diluted by air entering through the porous cigarette paper. However, the filter of filter-tipped cigarettes is surrounded by relatively nonporous paper, resulting in a higher content of carbon monoxide exiting from the proximal cigarette end. Perforations in the filter tip circumvent this problem and significantly reduce carbon monoxide yield (Hoffmann et al. 1980; Wald and Smith 1973).

Many investigators have measured COHb or carbon monoxide concentration in expired gas following cigarette smoking and compared the levels achieved in smoking brands with different nominal yields (see Table 1). An increase, decrease, or no change in carbon monoxide intake has been observed, depending on relative differences in cigarette design and experimental procedure. As expected, unventilated filter-tipped cigarettes produced higher COHb levels than those observed with unfiltered cigarettes (Wald et al. 1977). This is in agreement with information provided by smoking-machine assays (Wald et al. 1973), but the use of ventilated filter-tipped cigarettes may produce COHb levels similar to those observed with unfiltered cigarettes despite lower carbon monoxide

yields on smoking-machine assay (Wald et al. 1977). Comparison of cigarettes with a marked difference in nominal carbon monoxide yield usually results in a lower COHb level when the lower yielding brand is being smoked (Russell et al. 1973; Turner et al. 1974; Sutton et al. 1978; Ashton et al. 1979); but over the range of different carbon monoxide yields there is a poor correlation between levels of COHb and measured carbon monoxide yield. Similar information has been observed using expired carbon monoxide concentrations.

Nicotine Uptake

It has been long considered that nicotine might serve as a primary reinforcer of cigarette smoking and that smokers might adjust their smoking behavior to regulate their level of nicotine intake. Several investigators have measured the blood, urinary, or salivary levels of nicotine or its major metabolite cotinine during the smoking of cigarettes of varying nominal nicotine yields (see Table 1). A reduction in blood (Russell et al. 1975; Sutton et al. 1978; Ashton et al. 1979; Hill and Marquardt 1980) and urinary (Goldfarb et al. 1976; Ashton et al. 1979; Stepney 1981) nicotine levels or in plasma (Hill and Marquardt 1980; Stepney et al. 1981) and urinary (Ashton et al. 1979; Hill and Marquardt 1980) cotinine levels has generally been observed on switching to a cigarette with a lower nominal nicotine yield. However, smokers show variable degrees of compensation for the lower yield, as there is generally a poor relationship between nominal nicotine yield and measured blood nicotine levels (Russell et al. 1980; Sutton et al. 1982; Feyerabend et al. 1982; Benowitz et al. 1983).

Relating nominal nicotine yield and blood nicotine levels, Ashton et al. (1979) estimated that smokers compensated for about two-thirds of the difference in nominal yields when they switched from medium nicotine cigarettes to high or low nicotine brands. Using a stepwise multiple regression analysis of nicotine yield and blood nicotine concentration, Russell et al. (1980) observed a significant, but very weak, correlation ($r = 0.21$) between the two measurements, but the nominal nicotine yield of the cigarettes accounted for only 4.4 percent of the variability in blood nicotine concentrations. The use of absolute rather than logarithmic analysis in this study has been criticized (Kozlowski et al. 1982; Herning et al. 1983), and the criticism involved the problems of trying to predict doses to individuals rather than the dose to groups. In another study using log-linear regression analysis (Herning et al. 1983), a better correlation was observed between nominal nicotine yield and the increasing blood nicotine after smoking ($r = 0.5$), but this study used Kentucky reference cigarettes rather than commercial brands, and these low yield cigarettes have less nicotine in the unburned tobacco than commercial low yield brands. Such a relationship still accounted for

only 25 percent of the individual differences in blood nicotine levels, whereas 50 to 60 percent was accounted for by individual differences in smoking behavior (Herning et al. 1983).

Additional information on compensatory alterations in nicotine intake has been provided by studying the mouth exposure index, which is calculated from analysis of cigarette butts for nicotine content and a knowledge of the retention efficiency of the filter tip (Ashton and Watson 1970). Because the amount of nicotine retained by a filter is proportional to the amount that passes through, it is possible to estimate the amount of nicotine presented to the smoker from the nicotine content of the filter. Results using this index have revealed a greater variation between individual studies (see Table 1) than observed with blood nicotine measurements. This may be related to the fact that filter efficiency is usually determined by a machine, but retention of nicotine is also dependent on the way the cigarette is smoked; therefore, the retention efficiency of the filter may vary between smokers.

Role of Tar Content

The observations that smokers adapt their smoking behavior according to the nicotine delivery of a cigarette and that many of the toxic effects of smoking appear to be related to tar rather than nicotine content has led to the suggestion that altering the tar to nicotine ratio might produce a cigarette less hazardous to health (Russell 1976; Stepney 1981). A cigarette with a medium nicotine, low tar, and low carbon monoxide yield might be advantageous. While nicotine has been the component most extensively studied, it may not be the only substance responsible for the addictive power of tobacco. It is not possible to separate the effects of tar and nicotine in most studies, as their respective yields usually show a very close correlation.

Using research cigarettes providing three different yields of nicotine and two different yields of tar, Goldfarb et al. (1976) found evidence of compensation for nicotine but not for tar content. The authors urged cautious interpretation of the results because of the limited range of tar yields examined. Examining a large number of subjects smoking cigarettes of varying tar and nicotine yield, Wald et al. (1981) found that both tar and nicotine were significantly related to blood COHb, taken as an index of cigarette smoke inhalation. Two-way analysis of variance of the data indicated that after allowing for the effect of either tar or nicotine yield, the COHb index was no longer significantly influenced by the other. A cross-over study of medium tar smokers who were switched to low nicotine, low tar cigarettes and medium nicotine, low tar cigarettes has been reported by Stepney (1981). While the intake of carbon monoxide was least with the medium nicotine, low tar cigarette, the mouth exposure

index to tar was similar among the brands. Indeed, the pattern of smoking adopted by the subjects was more effective in reducing the difference in tar delivery between the cigarettes than in compensating for nicotine delivery. Further evidence indicating the importance of cigarette tar delivery in determining smoking behavior was reported by Sutton et al. (1982). Using multiple regression analysis, they observed that when nicotine yield was controlled, smokers of lower tar cigarettes had higher blood nicotine levels than smokers of higher tar cigarettes, indicating that they inhaled a greater volume of smoke. In contrast, when tar yield was controlled, smokers of lower nicotine cigarettes had lower blood nicotine concentrations than smokers of higher nicotine cigarettes, indicating that they inhaled less smoke. These results suggest some compensation for tar over and above any compensation for nicotine. It may be that nonpharmacologic, sensory stimulation by factors such as the flavor of cigarette smoke may be more important than nicotine in determining smoking behavior.

These new observations, especially on the role of tar delivery, require further investigation. Most published research consists of controlled switching experiments in which the subject smokes cigarettes of varying yields (see Table 1). Further studies of smoking behavior in subjects who have voluntarily chosen cigarettes of different yields are needed. The absence of an acceptable, palatable "standard" research cigarette continues to be an impediment to research in this area.

Variations in Pattern of Cigarette Smoke Inhalation

While cigarette smoking is the single most important factor in the development of COLD, the majority of smokers never develop clinically significant airflow obstruction (Fletcher et al. 1976). Despite the clear dose–response relationship between number of cigarettes smoked and death from COLD, attempts at identifying the individual susceptible smoker on the basis of number of cigarettes smoked have had very limited success.

Another approach to identifying the susceptible smoker is to study the manner of smoking, as this is probably a major determinant of the lung's exposure to cigarette smoke. Cigarette smoking consists of two phases: initially, the smoker takes a puff into the mouth, and after a variable 1 to 4 second pause, the smoke mixed with air is inhaled into the lungs (Rawbone et al. 1978; Higenbottam et al. 1980a; Tobin and Sackner 1982). Individual differences in the pattern of cigarette smoking such as the size of the puff volume, the duration of holding the smoke in the oral cavity before inhalation, and the depth and duration of inhalation are among the important factors determining the relative concentration of smoke constituents

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that reach the lung. Despite its significance in determining the distribution and deposition of cigarette smoke, the mode of inhalation following the puff has received scant scientific investigation.

A number of epidemiologic studies have examined the relationship between cigarette smoke inhalation, based on the smoker's subjective estimation, and the severity of pulmonary disease. Results of these studies are conflicting; some investigators reported an association between smoke inhalation and the presence of mucus hypersecretion (Rimington 1974; Schenker et al. 1982; Dean et al. 1978) and decline in pulmonary function (Ferris et al. 1976; Bosse et al. 1975), and others observed no relationship between inhalation and pulmonary dysfunction (Beck et al. 1981; Schenker et al. 1982). The inconsistencies in these epidemiologic studies may be due to the smokers' inability to accurately describe their inhalation pattern.

There are three reports of the relationship between subjective estimations of cigarette smoke inhalation and direct objective measurement. Rawbone et al. (1978) found that the rating on a visual analog scale was a good predictor of inhalation volume (r=0.65). Conversely, Tobin et al. (1982a) noted no relationship between inhalation volume and the smoker's perception of depth of inhalation, indicated on a visual analog scale (r=0.04); a similar finding was reported by Adams et al. (1983) (r=0.04). Standardizing the inhaled volume for vital capacity did not improve the relationship. Other investigators using measurements of COHb observed a weak relationship between self-estimated inhalation and COHb concentration (Stepney 1982; Wald et al. 1978). Measurements of COHb reflect the amount of cigarette smoke absorbed by the lung. In addition to being affected by the depth of inhalation, COHb concentration is influenced by the varying carbon monoxide yields of different cigarettes, the number of puffs per cigarette, puff volume, pulmonary function—particularly diffusing capacity and alveolar ventilation—and hemoglobin concentration (Wald et al. 1978; Rickert et al. 1980). Therefore, it yields valuable complementary information, but it does not provide a direct measure of the pattern of inhalation (Tobin et al. 1982a; Guyatt et al. 1983).

Direct measurements of the pattern of cigarette smoke inhalation have been reported for a small number of smokers. Initially, the puff from the cigarette is taken into the mouth, and after a variable pause of 1 to 4 seconds, it is inhaled into the lungs (Rawbone et al. 1978; Higenbottam et al. 1980a; Tobin and Sackner 1982; Tobin et al. 1982a; Adams et al. 1983). Higenbottam et al. (1980a) reasoned that this pause, while holding the smoke in the mouth, minimized the irritant qualities of cigarette smoke. In a group of five subjects who were requested to inhale smoke directly into their lungs, without an intervening pause in the mouth, consistent acute airway narrowing was observed. In contrast, smokers adopting the usual two-phase

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smoking pattern showed a variable airway response. The authors suggested that buccal absorption of water-soluble compounds, such as sulfur dioxide and acrolein, together with precipitation of tar, minimized the irritating qualities of cigarette smoke. They observed no relationship between the acute airway response and amount of smoke inhaled in the regular two-phase smokers, although there appeared to be a relationship in those directly inhaling smoke into their lungs. However, there is a marked discrepancy in the inhalation volumes reported in this study compared with the values reported in other studies of cigarette smoke inhalation, probably due to the inaccuracy of the magnetometers employed for the measurements; therefore, a statement regarding the relationship between depth of smoke inhalation and the acute airway response may be misleading.

The report that acute airway narrowing is uncommon after cigarette smoking is in disagreement with the findings of several investigators who have observed bronchoconstriction to be a common phenomenon after acute smoke exposure (Nadel and Comroe 1961; Sterling 1967; Da Silva and Hamosh 1981; Tobin et al. 1982a); however, it is certainly plausible that the response is greater in smokers who inhale smoke directly into the lungs than in two-phase smokers. The frequency of direct inhalation of cigarette smoke into the lungs is unknown. In a small study of 10 smokers, Tobin and Sackner (1982) observed 1 subject who showed an approximately 50 ml expansion of the abdominal compartment simultaneously with taking the puff from the cigarette.

Adams et al. (1983) studied the relationship between puffing, cigarette smoke inhalation, and partitioning of airflow between the nose and mouth in 10 smokers. After taking the puff into the mouth, two subjects actively exhaled 80 ml and 200 ml volumes, respectively, before the subsequent inhalation. In this situation, the volumes of smoke might be expelled from the mouth, and little, if any, would be available for subsequent inhalation into the lungs. The frequency of this smoking pattern was not given, but another report from the same laboratory (Rawbone et al. 1978) indicated that it was uncommon. There was marked intersubject variation in the partitioning of airflow between the nose and mouth during smoking, with four subjects inhaling almost exclusively through the mouth, four inhaling predominantly through the nose, and the other two demonstrating both patterns of inhalation. The importance of factors in determining whether cigarette smoke is inhaled as a bolus followed by a subsequent "chaser" of air or is evenly distributed throughout the inhaled volume of air remains to be determined.

Considerable discrepancies exist between published reports of the volume of air mixed with smoke that is inhaled into the lungs, with reported mean inhalation volumes of 34 to 152 ml (Higenbottam et